Docket No.: JJPR-0043 App No.: Not Yet Assigned Filed: Not Yet Assigned Title: DNA Encoding A Human Histamine Receptor of the H3 Subtype Inventors: Lovenberg et al Phone: (215) 568-3100

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1/9 Figure 1A

Nucleic Acid sequence human histamine H3 receptor (full sequence including untranslated regions) [SEQ.ID.NO.:5]

CCACGCGTCCGCCGGCTGCACGGTCGCACCGGCAGCGCTCAGGCTCCGG CTCCTCTCCGCTGCAGCAGCCGCGCTGCCGGCCCCACTGGGCTCGGATC CGGCCCCGGCCCCTCGGCACCGCCTGCTCTGGCCCCGGCCCCGGCCCCG CGCAAAGACGAGGCTCCCGGGCCGGGCCCCCCGGCCCAGCTCTC GGCCGCCCCTGCCCCGCGTCCCGGAGCCGCGTGAGCCTGCGGGGCCAT GGAGCGCGCCGCCGACGGGCCGCTGAACGCTTCGGGGGCGCTGGCGG GCGATGCGGCGGCGGGGGGGGGGGGGGCTTCTCGGCAGCCTGGACC GCGGTGCTGGCCGCTCATGGCGCTCATCGTGGCCACGGTGCTGGG CAACGCGCTGGTCATGCTCGCCTTCGTGGCCGACTCGAGCCTCCGCACCC AGAACAACTTCTTCCTGCTCAACCTCGCCATCTCCGACTTCCTCGTCGGC GCCTTCTGCATCCCACTGTATGTACCCTACGTGCTGACAGGCCGCTGGAC CTTCGGCCGGGCCTCTGCAAGCTGTGGCTGGTAGTGGACTACCTGCTGT GCACCTCCTCTGCCTTCAACATCGTGCTCATCAGCTACGACCGCTTCCTG TCGGTCACCCGAGCGGTCTCATACCGGGCCCAGCAGGGTGACACGCGGCG GGCAGTGCGGAAGATGCTGCTGGTGTGGGTGCTGGCCTTCCTGCTGTACG GACCAGCCATCCTGAGCTGGGAGTACCTGTCCGGGGGCAGCTCCATCCCC GAGGGCCACTGCTATGCCGAGTTCTTCTACAACTGGTACTTCCTCATCAC GGCTTCCACCCTGGAGTTCTTTACGCCCTTCCTCAGCGTCACCTTCTTTA ACCTCAGCATCTACCTGAACATCCAGAGGCGCACCCGCCTCCGGCTGGAT GGGGCTCGAGAGCCGGCCCGAGCCCCTCCCGAGGCCCAGCCCTC ACCACCCCACCGCCTGGCTGCTGGGGCTGCTGGCAGAAGGGGCACGGGG AGGCCATGCCGCTGCACAGGTATGGGGTGGGTGAGGCGCCGTAGGCGCT GAGGCCGGGAGCCACCTCGGGGGTGGCGGTGGGGGCGCTCCGTGGC TTCACCCACCTCCAGCTCCGGCAGCTCCTCGAGGGGCACTGAGAGGCCGC GCTCACTCAAGAGGGGCTCCAAGCCGTCGGCGTCCTCGGCCTCGCTGGAG AAGCGCATGAAGATGGTGTCCCAGAGCTTCACCCAGCGCTTTCGGCTGTC TCGGGACAGGAAAGTGGCCAAGTCGCTGGCCGTCATCGTGAGCATCTTTG GGCTCTGCTGGGCCCCATACACGCTGCTGATGATCATCCGGGCCGCCTGC CATGGCCACTGCGTCCCTGACTACTGGTACGAAACCTCCTTCTGGCTCCT GTGGGCCAACTCGGCTGTCAACCCTGTCCTCTACCCTCTGTGCCACCACA GCTTCCGCCGGGCCTTCACCAAGCTGCTCTGCCCCCAGAAGCTCAAAATC CAGCCCCACAGCTCCCTGGAGCACTGCTGGAAGTGAGTGGCCCACCAGAG CCTCCCTCAGCCACGCCTCTCTCAGCCCAGGTCTCCTGGGCATCTGGCCC TGCTGCCCCTACCCGGCTCGTTCCCCCAGGGGTGAGCCCCGCCGTGTCT

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GTGGCCCTCTTAATGCCACGGCAGCCACCCTGCCATGGAGGCGCCTTC CTGGGTTGGCCAGAGGCCCCTCACTGGCTGGACTGGAGGCTGGGTGGCC GGCCCTGCCCCCACATTCTGGCTCCACCGGGGAGGGACAGTCTGGAGGT CCCAGACATGCTGCCCACCCCTGCTGGTGCCCACCCTTCGCAGTTACTG GTTGGTGTTCTTCCCAAAGCAAGCACCTGGGTGTGCTCCAGGCTTCCTGC CCTAGCAGTTTGCCTCTGCACGTGCACACCCTGCACACCCCTGCACACA CCTGCACACCGTCCCTCTCCCCGGACAAGCCCAGGACACTGCCTTTGCTG CCTTCTGTCTCTTGCATAAGCCTCAGGCCTGGCCCTTTCACCCCTCTTCC CACCAACTCTCTCTCCCCCAAAAGTGTCAAGGGGCCCTAGGAACCTCGA AGCTGTTCTCTGCTTTTCCATTCTGGGTGTTTTCAGAAAGATGAAGAAGA AAACATGTCTGTGAACTTGATGTTCGTGGGATGTTTAATCAAGAGAGACA AAATTGCTGAGGAGCTCAGGGCTGGATTGGCAGGTGTGGGCTCCCACGCC CTCCTCCCTCAGGCTTCCGGCTGAGCTGTGCCAGCTGCTTCTGCC CACCCGCCTCTGGGCTCACACCAGCCCTGGTGGCCAAGCCTGCCCCGGC CACTCTGTTTGCTCACCCAGGACCTCTGGGGGGTTGTTGGGAGGAGGGGGC CCGCTGGGCCGAGGGTCCCAAGGCGTGCAGGGGCGTCCAGAGGAGGT GCCCGGGCAGGGCCGCTTCGCCATGTGCTGTGCACCCGTGCCACGCGCT CTGCATGCTCCTGTGCCCGCTGCGCTGCCCTGCAAACCGTGAGG

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Figure 2

Nucleic acid sequence human histamine H3 receptor (coding region) [SEQ ID NO:6] GGCGGCGGGGGGGGGCGCGCGCTTCTCGGCAGCCTGGACCGCGGTGCTGGCCGCGCT CATGGCGCTGCTCATCGTGGCCACGGTGCTGGGCAACGCGCTGGTCATGCTCGCCTTCGTG GCCGACTCGAGCCTCCGCACCCAGAACAACTTCTTCCTGCTCAACCTCGCCATCTCCGACT TCCTCGTCGCGCCCTTCTGCATCCCACTGTATGTACCCTACGTGCTGACAGGCCGCTGGAC CTTCGGCCGGGGCCTCTGCAAGCTGTGGCTGGTAGTGGACTACCTGCTGTGCACCTCCTCT GCCTTCAACATCGTGCTCATCAGCTACGACCGCTTCCTGTCGGTCACCCGAGCGGTCTCAT ACCGGGCCCAGCAGGTGACACGCGGCGGCAGTGCGGAAGATGCTGCTGGTGTGGGTG CTGGCCTTCCTGTACGGACCAGCCATCCTGAGCTGGGAGTACCTGTCCGGGGGCAGCT CCATCCCGAGGGCCACTGCTATGCCGAGTTCTTCTACAACTGGTACTTCCTCATCACGGC TTCCACCTGGAGTTCTTTACGCCCTTCCTCAGCGTCACCTTCTTTAACCTCAGCATCTACC TGAACATCCAGAGGCGCACCCGCCTCCGGCTGGATGGGGCTCGAGAGGCAGCCGGCCCCG AGCCCCTCCGAGGCCCAGCCTCACCACCCCCACGCTGGTGCTGGGGCTGCTGGC GGCGCTGAGGCCGGGGGGCGACCCTCGGGGGGTGGCGGTGGGGGCGCTCCGTGGCTTC GGGCTCCAAGCCGTCGGCGTCCTCGGCCTCGCTGAGAAGCGCATGAAGATGGTGTCCCA GAGCTTCACCCAGCGCTTTCGGCTGTCTCGGGACAGGAAAGTGGCCAAGTCGCTGGCCGT CATCGTGAGCATCTTTGGGCTCTGCTGGGCCCCATACACGCTGCTGATGATCATCCGGGCC GCCTGCCATGGCCACTGCGTCCCTGACTACTGGTACGAAACCTCCTTCTGGCTCCTGTGGG CCAACTCGGCTGTCAACCCTGTCCTCTGTGCCACCACAGCTTCCGCCGGGCCTT CACCAAGCTGCTCTGCCCCAGAAGCTCAAAATCCAGCCCCACAGCTCCCTGGAGCACTG **CTGGAAG**

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Figure 3

Amino acid sequence human histamine H3 receptor [SEQ.ID.NO.:7]

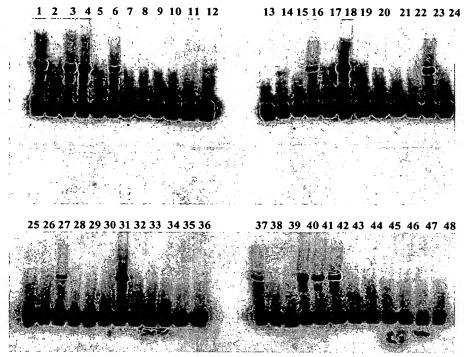
Met Glu Arg Ala Pro Pro Asp Gly Pro Leu Asn Ala Ser Gly Ala Leu Ala Gly Asp Ala Ala Ala Gly Gly Ala Arg Gly Phe Ser Ala Ala Trp Thr Ala Val Leu Ala Ala Leu Met Ala Leu Leu Ile Val Ala Thr Val Leu Gly Asn Ala Leu Val Met Leu Ala Phe Val Ala Asp Ser Ser Leu Arg Thr Gln Asn Asn Phe Phe Leu Leu Asn Leu Ala Ile Ser Asp Phe Leu Val Gly Ala Phe Cys Ile Pro Leu Tyr Val Pro Tyr Val Leu Thr Gly Arg Trp Thr Phe Gly Arg Gly Leu Cys Lys Leu Trp Leu Val Val Asp Tyr Leu Leu Cys Thr Ser Ser Ala Phe Asn Ile Val Leu Ile Ser Tyr Asp Arg Phe Leu Ser Val Thr Arg Ala Val Ser Tyr Arg Ala Gln Gln Gly Asp Thr Arg Arg Ala Val Arg Lys Met Leu Leu Val Trp Val Leu Ala Phe Leu Leu Tyr Gly Pro Ala Ile Leu Ser Trp Glu Tyr Leu Ser Gly Gly Ser Ser Ile Pro Glu Gly His Cys Tyr Ala Glu Phe Phe Tyr Asn Trp Tyr Phe Leu Ile Thr Ala Ser Thr Leu Glu Phe Phe Thr Pro Phe Leu Ser Val Thr Phe Phe Asn Leu Ser Ile Tyr Leu Asn Ile Gln Arg Arg Thr Arg Leu Arg Leu Asp Gly Ala Arg Glu Ala Ala Gly Pro Glu Pro Pro Pro Glu Ala Gln Pro Ser Pro Pro Pro Pro Pro Gly Cys Trp Gly Cys Trp Gln Lys Gly His Gly Glu Ala Met Pro Leu His Arg Tyr Gly Val Gly Glu Ala Ala Val Gly Ala Glu Ala Gly Glu Ala Thr Leu Gly Gly Gly Gly Gly Gly Ser Val Ala Ser Pro Thr Ser Ser Ser Gly Ser Ser Ser Arg Gly Thr Glu Arg Pro Arg Ser Leu Lys Arg Gly Ser Lys Pro Ser Ala Ser Ser Ala Ser Leu Glu Lys Arg Met Lys Met Val Ser Gln Ser Phe Thr Gln Arg Phe Arg Leu Ser Arg Asp Arg Lys Val Ala Lys Ser Leu Ala Val Ile Val Ser Ile Phe Gly Leu Cys Trp Ala Pro Tyr Thr Leu Leu Met Ile Ile Arg Ala Ala Cys His Gly His Cys Val Pro Asp Tyr Trp Tyr Glu Thr Ser Phe Trp Leu Leu Trp Ala Asn Ser Ala Val Asn Pro Val Leu Tyr Pro Leu Cys His His Ser Phe Arg Arg Ala Phe Thr Lys Leu Leu Cys Pro Gln Lys Leu Lys Ile Gln Pro His Ser Ser Leu Glu His Cys Trp Lys

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Figure 4

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PCR-based distribution of human histamine H3 receptor



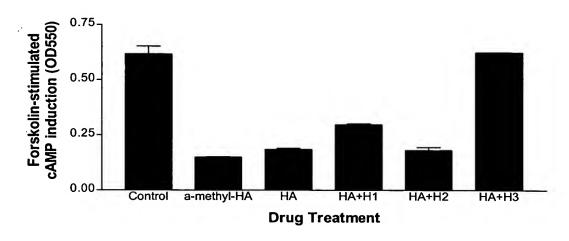
1, Amygdala; 2, Bone Marrow; 3, Brain; 4, Cerebellum; 5, Heart; 6, Hippocampus; 7, Kidney; 8, Liver; 9, Lung; 10, Pancreas; 11, Placenta; 12, Prostate; 13, Skeletal Muscle; 14, Small Intestine; 15, Spleen; 16, Spinal Cord; 17, Stomach; 18, Thalamus; 19, Testis; 20, Thymus; 21, Uterus; 22, Adrenal Gland; 23, Caudate Nucleus; 24, Lymph Node; 25, Mammary Gland; 26, Salivary Gland; 27, Substantia Nigra; 28, Thyroid; 29, Trachea; 30, Spleen; 31, Thalamus; 32, Placenta; 33, Heart; 34, Liver; 35, Lung; 36, Uterus; 37, Pituitary; 38, Spinal cord; 39, Bone Marrow; 40, Hippocampus; 41, Dorsal Root Ganglia; 42, Small Intestine; 43, Negative Control; 44, Negative Control; 45, Negative Control; 46, Negative Control; 47, Negative Control; 48, Negative Control.

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Figure 5

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Effect of H1, H2, or H3 antagonists on Histamine-induced inhibition of cAMP induction in H3-transfected L cells



a-methyl-HA = H3 agonist alpha-methyl-histamine (1uM)

HA = Histamine (1uM)

H1 antagonist = diphenhydramine (10uM) H2 antagonist = ranitidine (10uM)

H3 antagonist = thioperamide (10uM)

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Figure 6: Sequence of pH3R probe [SEQ.ID.NO.:8]

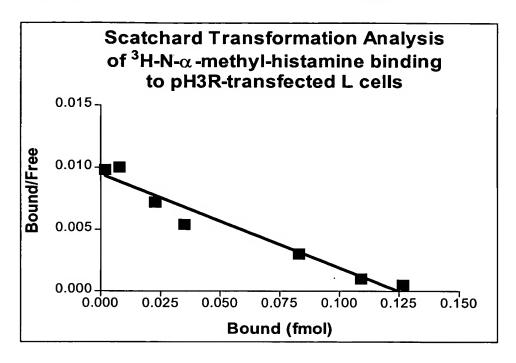
ACTGGTACGAAACCTCCTTCTGGCTCCTGTGGG<u>CCAACTCGGCTG</u>TCAACC CTGTCCTCTACCCTCTGTGCCACCACAGCTTCCGCCGGGCCTTCACCAAGC TGCTCTGCCCCAGAAGCTCAAAATCCAGCCCCACAGCTCCCTGGAGCAC TGCTGGAAGTGAGTGGCCCACCAGAGCCTCCCTCAGCCACGCCTCTCTCA GCCCAGGTCTCCTGGCCATCTGCCCCCTACCCGGCTCGTTCC CCCAGGGTGAGCCCGCGTGTCTGTGGCCCTCTCTTAATGCCACGGCA GCCACCCTGCCATGGAGGCCCCTTCCTGGGTTGGCCAGAGGGCCCCTCAC TGGCTGGACTGGAGGCTGGGTG

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FIGURE 7A

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FIGURE 7B

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